(b) a non-specific immune response enhancer;

and thereby stimulating and/or expanding T cells in a mammal.

REMARKS

Reconsideration of the above-identified application is respectfully requested. Claims 35-37, 39-55, 57, 63-69 are presently under consideration in this case. Claims 36, and 39-57 have been cancelled and claims 35, 37, 63, 65, 66, 68, and 69 have been amended for purposes of clarity and to advance prosecution of this application. It is urged that support for the above amendments can be found throughout the specification as originally filed and that none of the amendments constitutes new matter. It should also be noted that the above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter modified and/or removed in a related divisional, continuation and/or continuation-in-part application.

Rejection under 35 U.S.C. § 112, first paragraph (written description)

In section 5, the Examiner rejects claims 35-37, 39-55, 57, and 63-69 under 35 U.S.C. § 112 first paragraph. The Examiner alleges that due to the variant language of the claims, the written description in the specification is not commensurate with the scope of the claimed invention.

Without acquiescing to the Examiner's allegations, Applicants have amended the claims to recite methods of using a WT1 immunogenic portion consisting of SEQ ID NO:144, or a variant of SEQ ID NO:144 containing between 1 and 3 amino acid substitutions, wherein the ability of the variant to react with WT1-specific T-cells is not substantially diminished. Support for each element of the currently pending claims can be found throughout the applicants' specification as originally filed.

As for the "variant" language of the claims, these claims have been amended to specify that the WT1 compositions consist of the p130-138 immunogenic portion set forth in SEQ ID NO:144 or a variant thereof that differs from the immunogenic portion due to substitutions at between 1 and 3 amino acid positions within the immunogenic portion, such that

the ability of the variant to react with antigen-specific T-cell lines or clones is not substantially diminished. As described in the applicants' specification, p130-138 represents a naturally processed WT1 peptide epitope with motifs appropriate for binding to class I MHC, and was first identified using BIMAS HLA peptide binding prediction analyses (e.g., page 49, lines 11-14, and Tables V, XIII, XVI-XVII, XXIV, XXVI, XXVII, XXX, XXXII-XXXVII, and XLVI). Immunization with p117-139 peptide set forth in SEQ ID NO:2, which comprises p130-138 of SEQ ID NO:144, was demonstrated by the applicants to elicit a proliferative T cell response in vivo (e.g., page 47, line 24 through Page 48, line 7; also Figures 5A-5C). Moreover, the WT1-specific T cells stimulated in vivo were demonstrated, using a chromium release assay, to be capable of killing WT1 positive tumor cells, whereas no killing of WT1 negative tumor cells was observed (e.g., Example 5, page 100, line 14 through page 102, line 15). Furthermore, the applicants determined that, in particular, p130-138 of SEQ ID NO:144, is a naturally processed epitope that is recognized by WT1-specific T cells (e.g., page 102, lines 5-15). Thus, the applicants have identified T cells specific for SEQ ID NO:144 and that are capable of recognizing and lysing tumor cells expressing WT1.

Importantly, these WT1-specific T-cells identified by the applicants can be routinely isolated and used in the identification of the immunogenic variants of SEQ ID NO:144, such as recited in the present claims. For example, a series of variants of SEQ ID NO:144, having up to 3 amino acid substitutions, can be synthesized and compared with SEQ ID NO:144 in their ability to stimulate proliferation of the WT1-specific T-cells. As disclosed by the applicants, at page 15, lines 24-30:

> (T)he ability of a variant to react with antigen-specific antisera and/or T-cell lines or clones may be enhanced or unchanged, relative to the native polypeptide, or may be diminished by less than 50%, and preferably less than 20%, relative to the native polypeptide. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antisera and/or T-cells as described herein.

Applicants submit that the skilled artisan would readily understand, in light of the applicants' disclosure, the single identifying characteristic common to the claimed variants, i.e., their ability to stimulate T cells specific for SEQ ID NO:144, and would further appreciate the routine nature of the techniques used in their identification. Thus, in view of the applicants specification, and the routine and art recognized approaches for the identification and evaluation

of variants that are reactive with antigen-specific T-cells, the person of ordinary skill in the art would recognize that the applicants were indeed in possession of the presently claimed invention as of the filing date of the captioned application. Reconsideration of the Examiner's rejection under 35 USC 112, first paragraph is thus respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph (indefiniteness)

In section 6 of the Action, Claims 65 and 66 are rejected as being indefinite. The Examiner points out that claims 65 and 66 lack antecedent basis in claim 63 in the recitation of "wherein the bone marrow, peripheral blood or fraction is obtained." The typographical error in the dependency (claims 65 and 66 should depend from claim 64, not claim 63), has been corrected by the current amendments. Applicants submit that this ground for rejection has been obviated by the currently amended claims and thus request its withdrawal.

Rejections under 35 U.S.C. § 102(a), 102(b), or 102(e)

In sections 8 and 9 of the Action, the Examiner rejects claims 35-37, 39-42, 45, 49, 53, 55, 57, 63-65, 68, and 69 as being anticipated by Chada, *et al.* as evidenced by Berzofsky, *et al.*, and by Berzofsky, *et al.*. The Examiner alleges that Chada and Berzofsky teach a method of cancer immunotherapy wherein immunogenic WT1 peptides which stimulate T cell responses are administered to a patient and that said WT1 peptide is administered with a non-specific immune enhancer. The Examiner further alleges that Chada and Berzofsky teach the use of peptides which induce T cell mediated responses wherein the art recognizes that such peptides can have less than 16 amino acids. The Examiner goes on to allege that Chada and Berzofsky teach that the aforementioned peptide can be used to treat the WT1 positive Wilms' tumor. The Examiner alleges that the peptide taught by the above references comprises SEQ ID NO:144.

Chada teach the use of "altered cellular components" including various cellular products known to be involved in tumorigenesis, *e.g.* ras and WT1. Berzofsky teach generally on using peptides to elicit CTL response against cancer cells. There is no reference to any defined epitopes in the cited references, and no reference to the epitope consisting of SEQ ID NO:144 of the presently amended claims. Berzofsky teach the use of peptides to induce CTL responses. However, the length of known epitopes in the cited art is irrelevant given that Chada do not teach the claimed epitope, or any other epitope. While not acquiescing to the Examiner's

rejection, the presently amended claims are now directed to the use of compositions comprising an immunogenic portion of a native WT1, wherein the immunogenic portion consists of SEQ ID NO:144. Applicants submit that the presently claimed invention is indeed novel over the above cited references on the basis that these references fail to teach an immunogenic WT1 peptide consisting of SEQ ID NO:144, much less that the peptide is effective for eliciting immune responses, in particular CTL responses. The amended claims specify the use of the defined epitope set forth in SEQ ID NO:144, an epitope that has not been identified previously. Thus, the cited art would not anticipate that the particular peptide of WT1 of the instant claims is immunogenic and of particular importance for inducing immune responses against WT1.

In light of the above remarks and the presently amended and canceled claims, Applicants submit that this ground for rejection has thus been obviated and respectfully request its withdrawal.

Rejections under 35 U.S.C. § 103(a)

In Sections 11 and 12 of the Action, claims 35-37, 39-55, 57, 63-69 are rejected as being obvious over Chada, *et al.*, or Berzofsky, *et al.*, in view of Silberstein, *et al.*, or Inoue, *et al.* The Examiner sets forth arguments similar to those in the above rejections under § 102 in addition to arguing that, since Silberstein teaches that high levels of WT1 are expressed in certain types of breast cancers, and Inoue teaches that high levels of WT1 are expressed in certain types of leukemia, it would have been obvious to one of skill in the art to determine tumor specific epitopes in breast cancer and leukemia.

Applicants again note that the pending claims have been amended to specify the use of a WT1 immunogenic portion consisting of SEQ ID NO:144. Applicants' arguments to the Examiner's position regarding Chada, *et al.* as evidenced by Berzofsky, *et al.*, and by Berzofsky, *et al.*, are equally applicable in the context of this rejection under 35 U.S.C. 103(a). As set forth above, the cited references fail to teach the use of the specific WT1 immunogenic portions presently claimed by the applicants. Likewise, Silberstein et al. fails to teach the specific WT1 immunogenic portions presently claimed. Thus, all of the cited references fail to teach or suggest the presently claimed epitope of SEQ ID NO:144 or its use in the claimed methods. In view of this, applicants respectfully submit that the cited references, taken either alone or in combination, cannot reasonably render obvious the presently claimed use of WT1 immunogenic portion

consisting of SEQ ID NO:144, when the cited references offer no teaching or suggestion as to the existence and/or the identity of the now claimed use of said immunog nic portions. In light of these remarks, Applicants urge that this ground for rejection has been obviated and respectfully request withdrawal of the rejection.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with Markings to Show Changes Made."

All of the claims remaining in the application are now believed allowable.

Respectfully submitted,

Seed Intellectual Property Law Group PLLC

Jeffrey Hundley
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Enclosures:
Postcard
Check
Form PTO/SB/21
Form PTO/SB/17 (+ copy)
Petition for an Extension of Time

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Version with Markings to Show Changes Made

Claims 35, 37, 63, 65, 66, 68, and 69 have been amended as follow:

35. (Amended) A method for enhancing or inducing an immune response in a human patient, comprising administering to a patient a ~~pharmaceutical composition~~ comprising:

(a) a WT1 polypeptide ~~that comprises~~consisting of an immunogenic portion of a native WT1 or a variant thereof that differs from the immunogenic portion due to substitutions at between 1 and 3 amino acid positions within the immunogenic portion, ~~in one or more substitutions, deletions, additions and/or insertions~~ such that the ability of the variant to react with ~~antigen~~WT1-specific ~~antibodies and/or~~ T cell lines or clones is not substantially diminished, wherein the immunogenic portion consists of the consecutive amino acids of SEQ ID NO:144; and

(b) a physiologically acceptable carrier or excipient;

and thereby enhancing or inducing an immune response specific for WT1 or a cell expressing WT1 in the human patient.

37. (Amended) A method for enhancing or inducing an immune response in a human patient, comprising administering to a patient a ~~vaccine~~ composition comprising:

(a) a WT1 polypeptide ~~that comprises~~consisting of an immunogenic portion of a native WT1 or a variant thereof from the immunogenic portion due to substitutions at between 1 and 3 amino acid positions within the immunogenic portion, ~~that differs in one or more substitutions, deletions, additions and/or insertions~~ such that the ability of the variant to react with ~~antigen~~WT1-specific ~~antibodies and/or~~ T cell lines or clones is not substantially diminished, wherein the immunogenic portion consists of the consecutive amino acids of SEQ ID NO:144; and

(b) a non-specific immune response enhancer;

and thereby enhancing or inducing an immune response specific for WT1 or a cell expressing WT1 in the human patient.

63. (Amended) A method for stimulating and/or expanding T cells, comprising contacting T cells ~~with~~ a WT1 polypeptide, a polynucleotide encoding a WT1 polypeptide and/or an antigen presenting cell that expresses a WT1 polypeptide, wherein said WT1 polypeptide consists of an immunogenic portion of native WT1, or a variant thereof that differs from the immunogenic portion due to substitutions at between 1 and 3 amino acid positions within the immunogenic portion, such that the ability of the variant to react with WT1-specific T cell lines or clones is not substantially diminished, wherein the immunogenic portion consists of the consecutive amino acids of SEQ ID NO:144, under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

65. (Amended) A method according to claim 6~~4~~3, wherein the bone marrow, peripheral blood or fraction is obtained from a patient afflicted with a malignant disease associated with WT1 expression.

66. (Amended) A method according to claim 6~~4~~3, wherein the bone marrow, peripheral blood or fraction is obtained from a mammal that is not afflicted with a malignant disease associated with WT1 expression.

68. (Amended) A method for stimulating and/or expanding T cells in a mammal, comprising administering to a mammal a ~~pharmaceutical~~ composition comprising:

(a) one or more of:

(i) a WT1 polypeptide;

(ii) a polynucleotide encoding a WT1 polypeptide; or

(iii) an antigen-presenting cell that expresses a WT1 polypeptide;

wherein said WT1 polypeptide consists of an immunogenic portion of native WT1, or a variant thereof that differs from the immunogenic portion due to substitutions at between 1 and 3 amino acid positions within the immunogenic portion, such that the ability of the variant to react with WT1-specific T cell lines or clones is not substantially diminished, wherein the immunogenic portion consists of the consecutive amino acids of SEQ ID NO:144; and

(b) a physiologically acceptable carrier or excipient;

and thereby stimulating and/or expanding T cells in a mammal.

69. (Amended) A method for stimulating and/or expanding T cells in a mammal, comprising administering to a mammal a ~~vaccine~~ composition comprising:

(a) one or more of:

(i) a WT1 polypeptide;

(ii) a polynucleotide encoding a WT1 polypeptide; or

(iii) an antigen-presenting cell that expresses a WT1 polypeptide;

wherein said WT1 polypeptide consists of an immunogenic portion of native WT1, or a variant thereof that differs from the immunogenic portion due to substitutions at between 1 and 3 amino acid positions within the immunogenic portion, such that the ability of the variant to react with WT1-specific T cell lines or clones is not substantially diminished, wherein the immunogenic portion consists of the consecutive amino acids of SEQ ID NO:144; and

(b) a non-specific immune response enhancer;

and thereby stimulating and/or expanding T cells in a mammal.